III. REMARKS

Preliminary Remarks

Claims 14 and 35 are amended, and new claims 50-61 are added.

Claims 14 and 35 are amended to remove the terms "reactive against" and "and/or" that were objected to in the official action dated June 4, 2003. New claims 50-61 are directed to heterodimeric antibodies that comprise an antibody that binds specifically to CD20 and are capable of initiating programmed cell death (apoptosis), support for which is found in the specification; for example, on pages 35-37, which describe an assay performed with the claimed dimeric antibodies showing initiation of apoptosis of B cell lymphoma cells; and on pages 42-43, which describe a similar assay showing initiation of apoptosis of leukemic cells of a patient with chronic lymphocytic leukemia.

Patentability Remarks

35 U.S.C. §112, First Paragraph

Enablement

Claim 35 was rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable one skilled in the art to make or use the claimed invention, because the amino acid sequences of the constant regions of the light and heavy chains of antibodies C2B8 and p5E8 are not disclosed, and because of uncertainty regarding the public availability of cells containing plasmid TCAE-8 and having the ATCC designation 69119.

Applicants respectfully traverse the rejection of claim 35 under 35 U.S.C. 112, first paragraph. The amino acid sequences of the light and heavy chains of antibody C2B8, including the sequences of the human kappa and gamma-1 constant regions, are disclosed in Figures 1A and 2A of the present application. Moreover, Figures 2A-2C of U.S. Patent No. 5,736,137 also disclose nucleotide sequences of plasmid TCAE-8 that encode the constant regions of the human kappa light chain and the human gamma-1 heavy chain. Submitted

November 4, 1992, under the terms of the Budapest Treaty. The amino acid sequences of the

light and heavy chains of antibody p5E8 are disclosed in U.S. Patent No. 6,011,138, which also describes the light and heavy chains of antibody p5E8 as having human kappa and gamma-1 constant regions, respectively (cols. 25-34). In view of the foregoing, a person skilled in the art at the time the present application was filed would have been able to make and use DNA expression vectors encoding the light and heavy chains of antibodies C2B8 and p5E8 without undue experimentation. Withdrawal of the rejection of claim 35 under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

35 U.S.C. §112, Second Paragraph

Amended claims 14 and 35 do not use the terms "reactive against" or "and/or" that were the basis for rejecting claim 14 under 35 U.S.C. 112, 2nd paragraph. Withdrawal of the rejection under 35 U.S.C. 112, 2nd paragraph, is therefore respectfully requested.

35 U.S.C. §103(a)

Claims 1-2, 4-9, 14, 24-29, 34-36, 41, and 45-48 were rejected under 35 U.S.C. 103(a) as being obvious in view Caron et al. (1992), in view of Fanger et al. (1992), Cumber et al. (1992), U.S. Patent No. 6,011,138 (Reff et al.), Reff et al. (1994), and the 1994-95 Pierce Catalog (pages T-157, T-163-169). The initial statement of the rejection is found in the office action dated 8/28/02 (pp. 10-13).

The applicants respectfully traverse the rejection. None of the cited references, alone or in combination, describe or suggest the method for producing a heterodimeric antibody of independent claims 1 and 24, which comprises (a) obtaining a purified first antibody in which an amino acid in the heavy chain of an antibody is replaced with a cysteine, (b) contacting said purified first antibody with an amount of a reducing agent sufficient to partially reduce the disulfide bonds of said first antibody, and then (c) contacting said first antibody with a second antibody that contains a thiol reactive group other than a cysteine group introduced therein to produce an antibody heterodimer that retains its binding specificity following dimerization.

two such antibodies are cross-linked together through the sulfhydryls of the introduced

cysteines. The Cumber et al. reference similarly describes a method for homodimerization of antibody Fv fragments in which a cysteine is added to the C terminus of the heavy chain variable domain of an Fv fragment, and two such Fv fragments are cross-linked together through the sulfhydryls of the introduced cysteines. Fanger et al. describe chemically crosslinking antibodies of different types using bifunctional reagents that are reactive with ε-amino groups or hinge region SH groups (p. 102), and the 1994 Pierce Catalog is cited for its suggestion to perform molecular conjugation reactions using heterobifunctional crosslinking agents in order to reduce undesired polymerization or self-conjugation, to produce bispecific antibodies.

The office action fails to establish *prima facie* that it would have been obvious to one of ordinary skill in the art to practice the claimed method. The steps of the claimed method include (a) obtaining a purified first antibody in which an amino acid in the heavy chain is replaced with a cysteine, (b) contacting the purified antibody with an amount of a reducing agent sufficient to partially reduce the disulfide bonds of said first antibody, and then (c) contacting the first antibody with a second antibody that contains a thiol reactive group other than a cysteine group introduced therein, to produce a heterodimeric antibody that retains its binding specificity following dimerization. The specification describes the claimed method as providing approximately 100% increase in yield over a method such as that described in Caron et al., which does not include the step of contacting the first antibody with a reducing agent sufficient to partially reduce the disulfide bonds (see examples 1 and 2, pp. 25-27). The increased yield of antibody dimer produced by the claimed method was an unexpected and unpredictable result. At the time the invention was made, it was known that reducing agents reduce and cleave intra- and interchain disulfide bonds in antibodies (*e.g.*, see Cumber et al., p. 121, right column), and persons skilled in the art would reasonably have avoided contacting the antibodies with reducing agent prior to dimerization, in order to prevent the disassembly of the antibodies into their component polypeptides. Persons skilled in the art would therefore have regarded the prior art taught as teaching away from the claimed method, and the claimed method would not have been obvious to one of ordinary skill in the

IgG IgG heterodimer of claims 45-46, which comprises introducing a cysteine residue in a

first IgG MAb at a position which does not interfere with the antigen binding properties of said heterodimer, and which inhibits or prevents formation of an intramolecular disulfide bridge between sister heavy chains on the same antibody molecule. None of the cited references, alone or in combination, disclose or suggest this element of the invention.

In view of the foregoing, the Applicants submit that the claimed invention was not obvious to one of ordinary skill in the art in view of the cited references, and respectfully request that the rejection of the claims under 35 U.S.C. 103(a) in view of the prior art be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By 

Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40,944
Tel.: (703) 905-2144
Fax.: (703) 905-2500

PILLSBURY WINTHROP LLP
P.O. Box 10500

Attachments:

1. A substitute declaration and power of attorney.

2. A copy of the receipt showing that cells of the cell line having the ATCC designation 69119 containing plasmid TCAE-8 encoding the light and heavy chains of C2B8 were deposited with the American Type Culture Collection on November 4, 1992, under the terms of the Budapest Treaty.